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Combined Intravenous Thrombolysis and Thrombectomy vs Thrombectomy Alone for Acute Ischemic Stroke
A Pooled Analysis of the SWIFT and STAR Studies

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IMPORTANCE Mechanical thrombectomy (MT) improves clinical outcomes in patients with acute ischemic stroke (AIS) caused by a large vessel occlusion. However, it is not known whether intravenous thrombolysis (IVT) is of added benefit in patients undergoing MT.

OBJECTIVE To examine whether treatment with IVT before MT with a stent retriever is beneficial in patients undergoing MT.

DESIGN, SETTING, AND PARTICIPANTS This post hoc analysis used data from 291 patients treated with MT included in 2 large, multicenter, prospective clinical trials that evaluated MT for AIS (Solitaire With the Intention for Thrombectomy performed from January 1, 2010, through December 31, 2011, and Solitaire Flow Restoration Thrombectomy for Acute Revascularization from January 1, 2010, through December 31, 2012). An independent core laboratory scored the radiologic outcomes in each trial.

INTERVENTIONS Patients were treated with IVT with tissue plasminogen activator followed by MT (IVT and MT group) with the use of a stent retriever or MT with a stent retriever alone (MT group).

MAIN OUTCOMES AND MEASURES Successful reperfusion, functional independence (modified Rankin Scale score of 0-2) and mortality at 90 days, symptomatic intracranial hemorrhage, emboli to new territory, and vasospasm were compared.

RESULTS Of 291 patients included in the analysis, 160 (55.0%) underwent IVT and MT (mean [SD] age, 67 [13] years; 97 female [60.6%]), and 131 (45.0%) underwent MT alone (mean [SD] age, 69 [12] years; 71 [55.7%] female). Median Alberta Stroke Program Early CT Score at baseline was lower in the IVT and MT group (8 vs 9, $P = .04$). There was no statistically significant difference in the duration from symptom onset to groin puncture (254 minutes for the IVT and MT group vs 262 minutes for the MT group, $P = .10$). The number of passes, rate of successful reperfusion, functional independence at 90 days, mortality at 90 days, and emboli to new territory were also similar among groups. Symptomatic intracranial hemorrhage (1% vs 4%) and parenchymal hemorrhages type 1 (1% vs 3%) or type 2 (1% vs 2%) did not differ significantly ($P = .25$). Vasospasm occurred more often in patients who received IVT and MT vs MT alone (27% vs 14%, $P = .006$). In multivariate analysis, no statistically significant association was observed between IVT and MT vs MT alone for any of the outcomes.

CONCLUSIONS AND RELEVANCE The results indicate that treatment of patients experiencing AIS due to a large vessel occlusion with IVT before MT does not appear to provide a clinical benefit over MT alone. A randomized clinical trial seems warranted.

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Editorial page 259

Supplemental content

CME Quiz at jamanetworkcme.com and CME Questions page 368

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Five randomized trials published in 2015 have proven that mechanical thrombectomy (MT) with a stent retriever in combination with intravenous thrombolysis (IVT) is superior to IVT alone in patients experiencing acute ischemic stroke (AIS) caused by large vessel occlusion in the anterior circulation.[1-6] Before these studies,[1-6] IVT with tissue plasminogen activator (tPA) was the only reperfusion therapy with a proven benefit on clinical outcome in patients with AIS.[7] Overall, 85% of patients included in the MT trials received IVT before randomization for MT.[1-5] However, of those randomized to subsequent MT without follow-up computed tomographic angiography after IVT, only a small proportion of patients had vessel patency at the time of the first catheter angiography, suggesting that early recanalization in response to IVT is uncommon in this selected patient population with a proximal occlusion.[3] Despite the low frequency of early reperfusion with IVT alone, IVT could positively influence the clinical outcome after MT. For instance, by enhancing the fibrinolytic process, IVT could increase the speed and likelihood of successful reperfusion with MT, reduce the required number of passes with a stent retriever, and decrease the frequency of microvascular thrombosis.[8,9] Moreover, achieving recanalization is not always possible with MT, and such patients may still benefit from IVT. Finally, in some patients, especially those with distal occlusions, IVT alone may result in recanalization, averting the need for MT altogether. On the other hand, IVT may increase the risk of hemorrhagic complications[7,10] and result in fragmentation of the thrombus, potentially reducing the efficacy of MT in achieving complete reperfusion of distal vessels. In addition, use of IVT may cause a delay of the start of the MT procedure, especially if patients are first admitted to a primary stroke center and transferred to a comprehensive stroke center only after a large vessel occlusion has been established. Finally, IVT is a costly therapy, especially in the United States.[11]

A direct comparison between MT after IVT vs MT alone has not been studied in a randomized clinical trial to date. We therefore performed a post hoc analysis from a pooled data set from 2 large prospective clinical trials with independent neuroimaging assessment to determine the role of IVT in the treatment of patients with AIS caused by a proximal large vessel occlusion who were treated with MT.

Key Points

Question Is intravenous thrombolysis of added benefit to patients with acute ischemic stroke undergoing mechanical thrombectomy?

Findings This post hoc analysis used data from 291 patients treated with mechanical thrombectomy included in 2 large multicenter clinical trials; 55% received intravenous thombolysis in addition to mechanical thrombectomy, and 45% underwent only mechanical thrombectomy. After adjustment for potential confounders, no difference was found between the 2 groups in any of the clinical or radiologic outcomes studied.

Meaning This study found no apparent benefit of intravenous thrombolysis to patients with ischemic stroke undergoing mechanical thrombectomy.

Methods

Study Design and Population

We performed a patient-level, pooled, post hoc analysis of the Solitaire With the Intention for Thrombectomy (SWIFT) and Solitaire Flow Restoration Thrombectomy for Acute Revascularization (STAR) studies. The designs of both these multicenter, prospective clinical trial studies have been reported previously.[12,13] Briefly, both studies[12,13] included patients with AIS caused by a large vessel proximal arterial occlusion. In SWIFT, patients were randomized between MT with a Solitaire FR stent retriever (Medtronic Neurovascular) or the Merci device (Stryker Neurovascular).

This study had a roll-in phase in which all patients were treated with a stent retriever. This roll-in cohort was included in the current study. We excluded patients treated with the Merci device because this does not represent current clinical practice. STAR was a single-arm study in which all included patients underwent MT with the Solitaire FR stent retriever. In both SWIFT and STAR, patients were eligible if MT was feasible within 8 hours of symptom onset. Intravenous thrombolysis was recommended in all patients within 4.5 hours of stroke symptom onset who did not have any contraindication for IVT. In those not treated with IVT, the exact reason was not recorded in the case report form. To provide some insight into the possible reasons for withholding IVT, an overview of absolute and relative contraindications to IVT is provided. Clinical outcome was evaluated at 90-day follow-up using the modified Rankin Scale (mRS). SWIFT was active from January 1, 2010, through December 31, 2011, and STAR from January 1, 2010, through December 31, 2012. SWIFT was situated mainly in the United States and STAR in Europe, Canada, and Australia. The local ethics committee at every site approved the study protocol and informed consent form, and all patients or their legal representatives provided written informed consent.

The imaging data in STAR and SWIFT were adjudicated by independent core laboratories. Clinical outcomes were not centrally adjudicated across the 2 trials. Variables scored by the core laboratories were location of the occlusion, final reperfusion grades, and hemorrhagic complications. In SWIFT, the assessors were masked to allocation of the patient.

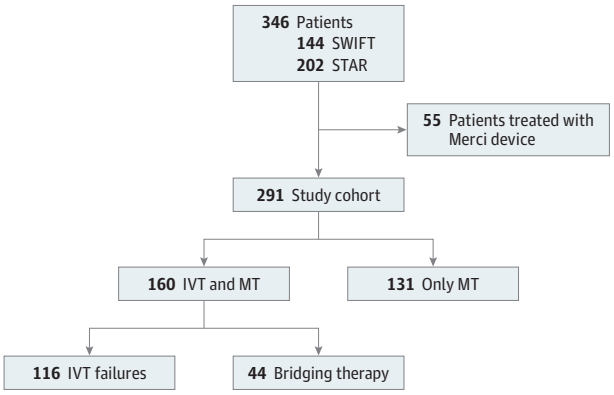
MT Procedure

The aim of the MT procedure in STAR and SWIFT was to achieve successful reperfusion of the territory of the occluded vessel as fast as possible. The use of a balloon guide catheter was mandatory, and rescue therapy with a different thrombectomy device or intra-arterial chemical thrombolysis was allowed if deemed necessary by the interventionalist. Follow-up brain imaging was performed after 24 hours in all patients.

Statistical Analysis

We compared patients who underwent MT after treatment with IVT to those who underwent MT alone. Successful

Figure. Flowchart of Patient Selection



A total of 346 patients were enrolled in the Solitaire With the Intention for Thrombectomy (SWIFT) (n = 144) and Solitaire Flow Restoration Thrombectomy for Acute Revascularization (STAR) (n = 202) clinical trial studies, of whom 55 patients were excluded from the analysis because they were not treated with the Solitaire FR (flow restoration) stent retriever. The remaining 291 patients comprised the analysis population.

reperfusion was defined as a modified Thrombolysis in Cerebral Infarction (mTICI) score of 2b or higher at the end of the procedure. We also analyzed separately the differences in mTICI 3 reperfusion between the groups because pretreatment with IVT could influence the frequency of small distal emboli. Symptomatic intracranial hemorrhage (sICH) was defined as any hemorrhage within 24 hours associated with an increase of 4 points or more on the National Institutes of Health Stroke Scale (NIHSS) or that resulted in death.

Categorical variables were compared between groups using a Fisher exact test. Continuous variables were compared using a *t* test, except in the case where medians and interquartile ranges are reported, in which case a Wilcoxon rank sum test was used. Using multivariate logistic regression analysis, we examined whether the use of IVT was associated with technical aspects, complication rate, or outcome after MT. The following clinical outcomes were included as dependent variables in separate models: mRS score of 0 to 2 (good clinical outcomes), mRS scores of 0 to 1 (excellent outcomes), and mortality at 90-day follow-up. In these models, we adjusted for age, sex, NIHSS score, Alberta Stroke Program Early CT Score (ASPECTS), location of occlusion, atrial fibrillation, diabetes, site of recruitment, and time from symptom onset to hospital arrival. To determine an association with technical aspects of the procedure and safety end points, we used the following parameters as dependent variables: more than 2 passes with stent retriever, mTICI 2b or 3 reperfusion, mTICI 3 reperfusion, sICH, emboli to uninvolved territory, atrial fibrillation, diabetes, site of recruitment, and vasospasm. Finally, for an association with procedural times, we used as dependent variables time from hospital arrival to groin puncture of less than 90 minutes and time from groin puncture to reperfusion of less than 45 minutes. These models were adjusted for age, sex, NIHSS score, ASPECTS, location of occlusion, atrial fibrillation, diabetes, site of recruitment, and time from symptom onset to hospital arrival. In a sensitivity analysis, we ran all multivariate analyses excluding patients who received bridging-dose tPA. SAS statistical software, version 9.1 (SAS Institute Inc), was used for analysis. Statistical significance was defined as 2-sided $P < .05$.

Results

In total, 346 patients were enrolled in SWIFT (n = 144) and STAR (n = 202) (**Figure**). Fifty-five patients from SWIFT randomized to treatment with the Merci device were excluded from the analysis. Of the remaining 291 patients, 160 (55.0%) underwent MT after IVT (mean [SD] age, 67 [13] years; 97 female [60.6%]), and 131 (45.0%) were treated with MT alone (mean [SD] age, 69 [12] years; 71 [55.7%] female). Of the patients who received IVT, IVT failed in 116 (full tPA dose), and 44 received bridging therapy. The mean tPA dose in patients who received bridging therapy was 0.62 mg/kg. The contraindications for IVT in patients who were treated with MT alone are reported in **Table 1**. Overall, 117 patients (89.3%) who did not receive IVT had at least one contraindication.

The baseline characteristics are provided in **Table 2**. Patients who received IVT and MT had a lower frequency of cardioembolic stroke attributable to atrial fibrillation (53 [33.1%] vs 62 [47.3%], $P = .02$) and diabetes (22 [13.8%] vs 32 [24.4%], $P = .02$) and had lower median ASPECTS (8 vs 9, $P = .04$) compared with patients who were treated with MT alone. No differences were found in median NIHSS scores (17 in both groups) or occlusion location between groups. Differences in baseline variables between patients included in SWIFT and STAR are provided in eTable 1 in the Supplement. A comparison of baseline characteristics, procedure details, and outcome between patients who received full-dose tPA and those who received bridging-dose tPA is given in eTables 2 and 3 in the Supplement.

Details of the MT procedure and clinical outcomes are presented in **Table 3**. The median time from symptom onset to hospital arrival was shorter in patients treated with IVT and MT (171 vs 190 minutes, $P = .04$), but the median time from hospital arrival to groin puncture was similar in both groups (79 vs 77 minutes, $P = .46$). No differences were found in the median number of passes (1 for both groups) or the rate of mTICI 2b or 3 reperfusion (127 [84.1%] vs 105 [84.7%]) among groups. Vasospasm occurred more often in patients who received IVT and MT (43 [26.9%] vs 18 [13.7%], $P = .006$). We found that sICH occurred less frequently in patients treated with IVT and MT (2 [1.3%] vs 5 [3.8%], $P = .25$), but the difference was not statistically significant. Frequency of other types of ICH was as follows: parenchymal hemorrhage type 1, 1 (0.6%) vs 4 (3.1%); parenchymal hemorrhage type 2, 1 (0.6%) vs 2 (1.5%); hemorrhagic infarct 1, 29 (18.1%) vs 25 (19.1%); hemorrhagic infarct 2, 19 (11.9%) vs 11 (8.4%); and subarachnoid hemorrhage, 2 (1.3%) vs 4 (3.1%). None of these differed significantly between groups (Table 3).

Results of the multivariate analyses are presented in **Table 4**. We did not find a statistically significant association between the use of IVT and any of the outcomes studied. There was a lower risk of sICH (adjusted odds ratio [OR], 0.03; 95% CI, 0.00-1.28), a higher risk of emboli to uninvolved territory

(adjusted OR, 4.12; 95% CI, 0.75-22.54), and a higher rate of functional independence (90-day mRS score of 0-2: adjusted OR, 1.48; 95% CI, 0.80-2.74) in patients treated with IVT and MT, although these findings were not statistically significant. When we excluded patients who received bridging-dose tPA, the results of the multivariate analysis were essentially the same (eTable 4 in the Supplement).

Discussion

Using data from 2 large international prospective studies, we examined whether treatment of patients with AIS with IVT before endovascular clot retrieval with the Solitaire FR stent retriever is beneficial or adds any risks to the procedure. Our results indicate that, after adjustment for confounders, the combination of IVT and MT had no statistically significant benefit over MT alone in terms of procedural, clinical, or safety outcomes.

Only a few studies[14-19] have previously examined differences between endovascular therapy combined with IVT vs endovascular treatment alone. Bhatia et al[14] analyzed data from 157 patients included in the Calgary Stroke Program between 2002 and 2009. They observed a trend toward a higher rate of recanalization and a lower rate of sICH among patients treated with intra-arterial IVT compared with patients treated only with intra-arterial therapy. There were important imbalances regarding endovascular technique and times to treatment between groups in this study, which make the data somewhat difficult to interpret. A different retrospective, single-center study[15] also found no difference between IVT and MT vs MT alone, but again this study had a limited sample size and did not adjust for confounding variables. A US phase 1 trial in which patients were randomized to IVT or placebo in combination with intra-arterial therapy found slightly higher recanalization rates among patients randomized to IVT.[16] This study included only 35 patients and used intra-arterial thrombolysis instead of MT, making it no longer clinically relevant. In a recent study, Broeg-Morvay and colleagues[17] used propensity score matching to compare 40 patients treated with MT with 40 patients who underwent MT

Table 1. Contraindications for IVT

Contraindication	No. (%) of Patients Undergoing MT without IVT (n = 131)
Oral anticoagulation or INR >1.7	38/122 (31.1)
Symptom onset to hospital arrival >4 h	40/124 (32.3)
Systolic blood pressure ≥185 mm Hg	11/129 (8.5)
Diastolic blood pressure ≥110 mm Hg	3/129 (2.3)
Glucose >400 mg/dL	1/126 (0.8)
Glucose <50 mg/dL	5/126 (4.0)
Platelets <100 × 103/μL	2/131 (1.5)
APTT >39 s	9/111 (8.1)
Prior stroke or TIA and diabetes	8/131 (6.1)

Abbreviations: APTT, activated partial thromboplastin time; INR, international normalized ratio; IVT, intravenous thrombolysis; MT, mechanical thrombectomy; TIA, transient ischemic attack.

SI conversion factors: To convert glucose to millimoles per liter, multiply by 0.0555; platelets to 10^9/L, multiply by 1.

Table 2. Baseline Characteristics of the Study Patients[a]

Characteristic	MT and IVT (n = 160)	MT Alone (n = 131)	*P* Value
Age, mean (SD), y	67 (13)	69 (12)	.14
Female	97/160 (60.6)	73/131 (55.7)	.41
NIHSS, median (IQR)	17 (13-20)	17 (13-20)	.86
Medical history			
Atrial fibrillation	53/160 (33.1)	62/131 (47.3)	.02
Hypertension	99/160 (61.9)	87/131 (66.4)	.46
Diabetes	22/160 (13.8)	32/131 (24.4)	.02
Hyperlipidemia	69/160 (43.1)	57/131 (43.5)	>.99
Current smoker	21/160 (13.1)	19/131 (14.5)	.74
Prior stroke or TIA	25/160 (115.6)	30/131 (22.9)	.13
Antiplatelet use	37/160 (23.1)	40/131 (30.5)	.18
Systolic blood pressure, mean (SD), mm Hg	145 (23)	147 (25)	.49
Diastolic blood pressure, mean (SD), mm Hg	80 (15)	80 (15)	.86
Left side occlusion	78/157 (49.7)	64/129 (49.6)	>.99
ASPECTS, mean (SD)	8.1 (1.8)	8.5 (1.6)	.03
ASPECTS, median (IQR)	8.0 (7.0-10.0)	9.0 (8.0-10.0)	.04
Location of occlusion			
Carotid	31/153 (20.3)	23/129 (17.8)	.72
M1	99/153 (64.7)	88/129 (68.2)	
M2 or M3	23/153 (15.0)	17/129 (13.2)	
Posterior circulation	0/153 (0)	1/129 (0.8)	
Serum glucose, mean (SD), mg/dL	126 (50)	130 (64)	.56
Platelets, mean (SD), ×10^3/μL	228 (74)	239 (85)	.23

Abbreviations: ASPECTS, Alberta Stroke Program Early CT score; IQR, interquartile range; IVT, intravenous thrombolysis; MT, mechanical thrombectomy; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.

SI conversion factors: To convert glucose to millimoles per liter, multiply by 0.0555; platelets to 10^9/L, multiply by 1.

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

Table 3. Details of Procedural, Clinical, and Safety Outcomes[a]

Variable	MT and IVT (n = 160)	MT Alone (n = 131)	*P* Value
Times, median (IQR), min			
Symptom onset to hospital arrival	171 (75-245)	190 (108-274)	.04
Symptom onset to groin puncture	254 (195-305)	262 (201-375)	.10
Hospital arrival to groin puncture	79 (49-111)	77 (54-120)	.46
Symptom onset to reperfusion	308 (253-361)	315 (242-424)	.15
No. of passes with stent retriever, mean (SD)	1.7 (0.9)	1.8 (1.0)	.28
No. of passes with stent retriever, median (range)	1 (1-5)	1 (1-7)	.30
mTICI 2b or 3 reperfusion	127/151 (84.1)	105/124 (84.7)	>.99
mTICI 3	86/151 (57.0)	66/124 (53.2)	.54
Rescue therapy	20/160 (12.5)	17/131 (13.0)	>.99
Complications			
Emboli to uninvolved territory	7/156 (4.5)	3/126 (2.4)	.52
Device-related serious adverse events	8/160 (5.0)	8/131 (6.1)	.80
Vasospasm	43/160 (26.9)	18/131 (13.7)	.006
sICH	2/160 (1.1)	5/131 (3.8)	.25
SAH	2/160 (1.1)	4/131 (3.1)	.41
PH1	1/160 (0.6)	4/131 (3.1)	.18
PH2	1/160 (0.6)	2/131 (1.5)	.59
HI1	29/160 (18.1)	25/131 (19.1)	.88
HI2	19/160 (11.9)	11/131 (8.4)	.44
Remote ICH	1/160 (0.6)	0/131 (0)	>.99
Vessel perforation	0/160 (0)	1/131 (0.8)	.45
Groin hematoma	3/160 (1.9)	2/131 (1.5)	>.99
Outcome at 90 d			
mRS score of 0-1[b]	65/156 (41.7)	46/128 (35.9)	.33
mRS score of 0-2[b]	90/156 (57.7)	61/128 (47.7)	.10
Mortality	13/160 (8.1)	16/131 (12.2)	.32

Abbreviations: HI, hemorrhagic infarct; IQR, interquartile range; IVT, intravenous thrombolysis; mRS, modified Rankin Scale; MT, mechanical thrombectomy; mTICI, modified Thrombolysis in Cerebral Infarction; PH1, parenchymal hemorrhage type 1; SAH, subarachnoid hemorrhage; sICH, symptomatic intracranial hemorrhage.

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

[b] Scores of 0 to 1 indicate excellent outcomes; 0 to 2, good outcomes.

after treatment with IVT. They also did not find any statistically significant differences in functional outcome or risk of sICH between the groups. However, unlike our study, they observed a trend toward a lower risk of sICH in the MT alone group. Weber et al[18] reported data from 250 patients treated with second-generation devices included in a retrospective, single-center study. Of these, 105 received IVT and 145 underwent MT alone. They did not find differences in successful revascularization rates (TICI 2b or 3, 73.8% vs 73.1%; *P* = .95), complications, or good clinical outcome (mRS scores of 0-2, 35.2% vs 40.0%; *P* = .44). In the MT alone group, 70 patients were potentially eligible for IVT but did not receive it intentionally. Comparing these patients with the 75 patients treated with MT alone with a contraindication to IVT, the authors found that the former group had better clinical outcomes (48.6% vs 32.0%, *P* = .04). Finally, they reported workflow measures showing shorter symptom onset to groin puncture, first imaging to groin puncture, and symptom onset to end of procedure in the MT alone group. A recent study by Leker et al[19] found that in patients treated with IVT and MT, fewer stent retriever passes were required to achieve recanalization than in patients who received MT alone. Although this finding would be in line with the hypothesis that IVT facilitates thrombus removal with MT, we could not confirm this observation. In our study, no difference was found in the median number of passes between the 2 groups.

Subgroup analyses in the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN), Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE), and Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours (REVASCAT) did not suggest statistical heterogeneity of the effect of MT between patients who did or did not receive IVT. Interestingly, in ESCAPE, MT was associated with an increase in mortality at 90 days in patients who did not receive IVT (20% vs 13%), whereas among patients who received IVT (as well as in the study as a whole), MT resulted in a decrease in mortality (7% vs 21%).[3] For MR CLEAN, an analysis of mortality stratified by IVT status has not been published to date. In REVASCAT, the effect size of MT was slightly higher in patients not treated with IVT but without statistical heterogeneity.[5] The subgroup analyses in these studies, however, were restricted by a small sample size: only 30 patients (13%) in MR CLEAN, 45 patients (27%) in ESCAPE, and 33 patients (32%) in REVASCAT underwent MT without IVT. The subgroup analyses were also not adjusted for case mix. The additional value of IVT could not be examined in the Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-arterial (EXTEND-IA) and Solitaire FR With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke (SWIFT PRIME) because treatment with IVT was mandatory for inclusion in these trials.

Table 4. Multivariate Analyses

Variable	No. (%) of Patients		OR (95% CI)	
	MT and IVT (n = 160)	MT Alone (n = 131)	Unadjusted	Adjusted
Times[a]				
Hospital arrival to groin puncture ≤90 min	97/156 (62.2)	72/121 (59.5)	1.12 (0.69-1.82)	1.63 (0.83-3.21)
Groin puncture to reperfusion ≤45 min	82/152 (53.9)	59/118 (50.0)	1.17 (0.72-1.90)	1.31 (0.75-2.29)
Technical details of the MT procedure[b]				
mTICI 2b or 3	127/151 (84.1)	105/124 (84.7)	0.96 (0.50-1.84)	0.68 (0.28-1.66)
mTICI 3	86/151 (57.0)	66/124 (53.2)	1.16 (0.72-1.87)	1.38 (0.76-2.51)
>3 Passes with stent retriever	30/132 (22.7)	30/120 (25.0)	0.88 (0.49-1.58)	0.90 (0.44-1.85)
Procedural complications[b]				
sICH	2/160 (1.3)	5/131 (3.8)	0.32 (0.06-1.67)	0.03 (0.00-1.28)
Emboli to uninvolved territory	7/156 (4.5)	3/126 (2.4)	1.93 (0.49-7.61)	4.12 (0.75-22.54)
Vasospasm	40/160 (25.0)	17/131 (13.0)	2.24 (1.20-4.17)	1.41 (0.58-3.42)
Outcome at 90 d[c]				
mRS scores of 0-2[d]	90/156 (57.7)	61/128 (47.7)	1.50 (0.94-2.40)	1.48 (0.80-2.74)
Mortality	13/160 (8.1)	16/131 (12.2)	0.64 (0.29-1.37)	0.90 (0.35-2.30)

Abbreviations: IVT, intravenous thrombolysis; mRS, modified Rankin Scale; MT, mechanical thrombectomy; mTICI, modified Thrombolysis in Cerebral Infarction; OR, odds ratio; sICH, symptomatic intracranial hemorrhage.

[a] Adjusted for age, sex, National Institutes of Health Stroke Scale (NIHSS) score, Alberta Stroke Program Early CT Score (ASPECTS), location of occlusion, atrial fibrillation, diabetes, site of recruitment, and interval from symptom onset to hospital arrival.

[b] Adjusted for age, sex, NIHSS score, ASPECTS, location of occlusion, international normalized ratio, antiplatelet use, atrial fibrillation, diabetes, site of recruitment, and systolic blood pressure.

[c] Adjusted for age, sex, NIHSS score, ASPECTS, location of occlusion, atrial fibrillation, diabetes, site of recruitment, and interval from symptom onset to hospital arrival.

[d] Scores of 0 to 2 indicate good outcomes.

In a recent published pooled analysis of MR CLEAN, SWIFT PRIME, EXTEND-IA, ESCAPE, and REVASCAT (Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke collaboration), no differences were found in clinical outcomes between IVT and MT and MT alone.[6]

One of the main reasons to use IVT in patients with a proximal occlusion is that it may lead to early recanalization, thereby negating the requirement for MT. However, data from recent trials suggest that such early recanalization does not occur often. In ESCAPE, only 8 of 165 patients (4.8%) randomized to MT had TICI 2b or 3 on the first angiography run.[3] These data were not stratified to IVT status, but even if all 8 patients were in the group that received IVT, the proportion of patients with early reperfusion would still be only 6.7%. Similar results were seen in MR CLEAN, where recanalization was found in 8 (3.7%) of 216 patients who underwent catheter angiography.[2] Eight other patients randomized to MT did not undergo catheter angiography because of clinical improvement. Again, assuming the artery had recanalized in all these patients, the proportion of patients with early reperfusion would still be less than 7%. Similar percentages of early reperfusion were observed in REVASCAT and SWIFT PRIME.[4,5] The chance of early recanalization in response to IVT is dependent on the location of the occlusion, with distal ICA occlusions responding poorly compared with M2 or M3 occlusions.[20,21] The fact that IVT often results in reperfusion of the occluded vessel over time was nicely illustrated in the ESCAPE study. In the control group, follow-up computed tomographic angiography was performed in 138 patients after a median period of 7 hours after symptom onset. Among those treated with IVT, recanalization was observed in approximately one-third of patients compared with only 7% of patients not treated with IVT.[3] However, the clinical benefit of this late reperfusion is unknown.

Strengths and Limitations

Strengths of our study include the large sample size, completeness of the data, and the use of independent adjudication committees. Several limitations also warrant comment. First, patients were not randomized for the use of IVT. Patients who underwent MT alone usually had a contraindication for IVT that may have affected their outcomes. We adjusted for baseline imbalances in the multivariate analyses, but still we cannot exclude the possibility of residual confounders. Second, although imaging end points were evaluated by an independent core laboratory in each trial, these outcomes were not centrally adjudicated across the 2 trials. Third, although we did not observe any statistically significant differences between the groups for any of the outcomes, we cannot exclude the possibility that this is attributable to the relatively small sample size. For instance, the point estimate of functional outcome and the rate of sICH were in favor of patients treated with MT and IVT, but the wide CIs preclude us from drawing firm conclusions. The finding that IVT was associated with a lower risk of ICH, a somewhat counterintuitive observation, should especially be interpreted with caution, given the low number of patients with a sICH in either group. Fourth, not all patients in the IVT and MT group were treated with the same tPA dose. Approximately a quarter of these patients received bridging-dose tPA (0.6 mg/kg), as used in the Interventional Management of Stroke II study.[22] A sensitivity analysis

excluding patients treated with bridging-dose tPA essentially revealed similar results. Fifth, roughly one-third of the patients who did not received tPA did not have a contraindication for IVT. This finding reflects the fact that local treatment protocols in some of the participating centers allowed direct treatment with MT in patients who were eligible for treatment with IVT.

Conclusions

We observed no benefit or harm of treatment with IVT and MT compared with MT alone in patients with AIS and a proximal occlusion. On the basis of these data, we believe that a randomized clinical trial directly comparing both strategies is warranted.

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